REMARKS/ARGUMENTS

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of three months of the period for response to the Office Action. The prescribed fee is enclosed.

The Examiner objected that the attempt to incorporate subject matter by reference to Application No. 08/923,558 is improper because the method of immunizing the mice is considered essential practise of the invention.

In this regard, it is noted that US Application No. 08/923,558 has proceeded to grant as US Patent No. 6,060,308 while Applications Nos. 08/476,397 and 08/896,500, also mentioned by the Examiner, also have proceeded to grant as US Patent Nos. 6,019,397 and 6,017,897 respectively.

In view of the grant of the three US Patents, it is submitted that specific recitation of the comparative data in this application is not required and the Examiner is requested to reconsider this matter.

The Examiner noted that the blanks on pages 23 and 24 have been filled in with reference to US Patent Application No. 09/190,245 filed November 13, 1998. The Examiner requested that the status of the application be updated to indicate it to be abandoned. However, the application still is pending according to the undersigned's records.

The Examiner considered the addition of the ATCC deposit 203461 deposited November 18, 1998 to be new matter. Reconsideration is requested having regard to the following comments.

The ATCC deposit form with respect to such deposit is enclosed. The specification contains the statement that the vectors have been deposited under the Budapest Treaty (confirmed by the enclosed deposit form), the samples of the deposited plasmid will become available to the public upon grant of a patent based on this United States Patent application and all restrictions or access to the deposit will be removed at that time. It is also stated that non-viable deposits will be replaced.

The entity "Pasteur Merieux Connaught" is a trading style of the assignee Connaught Laboratories Limited, of the same address. It is noted from the deposit form that the deposits were received by ATCC on November 12, 1998, i.e.

prior to applicants filing date of November 13, 1998. The deposited plasmid 203461 was clearly in the possession of the assignee and applicants at the time of filing.

Having regard to the above, it is submitted that applicants have fully satisfied the deposit requirements and the objection of new matter should be withdrawn.

The Examiner objected to the language of claim 11. Applicants had previously indicated that claim 11 had been deleted but inadvertently omitted instructions to do so. The claim now has been deleted, thereby obviating the objection.

The Examiner rejected claims 1, 6 to 19 and 36 to 38 under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had provision of the claimed invention. Reconsideration is requested, having regard to the following comments.

The Examiner indicated, in this regard, that claim 1 recites a protein fragment that induces production of antibodies that specifically react with the RSV protein. The Examiner asserts that the specification does not provide written description any such fragments. Claim 1 has been further amended to recite the feature of previous claim 7 and now recites that the fragment is a truncated RSV F or RSV G protein lacking the transmembrane anchor and cytoplasmic tail for which there is clear written description.

Having regard thereto, it is submitted that claim 1, 6 to 19 and 36 to 38 can no longer be considered to lack a written description and hence the rejection thereof under 35 USC 112, first paragraph, on this ground, should be withdrawn.

The Examiner rejected claims 1, 6 to 19 and 36 to 38 under 35 USC 112, first paragraph, because the specification, while enabling for immunogenic compositions, does not reasonably provide enablement for enhancing the immunoprotective ability of the paramyxovirus protein when expressed *in vivo* in a host. The Examiner considers that the specification does not enable a person skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record. Recons9ideration is requested, having regard to the following discussion.

The Examiner asserts that nowhere in the specification is the specific antibody response in mice shown to be protective. Protective data is present in Example 3. As clearly shown therein, mice were immunized with plasmid pMP44 without cardiotoxin pretreatment and were challenged. As indicated on page 24, immunization with pMP44 protected 5 out of 6 mice against live RSV challenge, a high level of protection. This level of protection was contrasted with that obtained using the SFV-RSV F RNA construct from USP 6,060,308 (Appln No. 08/923,558) which afforded no protection in the absence of cardiotoxin pretreatment. As shown in that patent, with cardiotoxin pretreatment, 100% protection was achieved using the SFV-RSV F RNA construct (see Table 2, col. 14, Group 2). Clearly, an even higher level of protection can be expected for applicants construct if cardiotoxin pretreatment is effected.

Accordingly, it is submitted that applicants data provides clear enablement of enhanced immunoprotective ability and an immunoeffective amount of the vector. It is submitted that the claims are fully enabled in this respect.

The Examiner further indicates that the specification does not teach any fragments of the F or G proteins that induce production of antibodies. As noted above, claim 1 has been limited to the fragment being the truncated RSV F or RSV G protein lacking the transmembrane anchor and cytoplasmic tail. pMP44 contains the nucleic acid encoding the fragment from RSV F protein.

Accordingly, it is submitted that the RSV fragment now defined in claim 1 is fully enabled.

Having regard to the above discussion, it is submitted that claims 1, 6 to 19 and 36 to 38, insofar as they remain in the application and in their amended form, are fully enabled and hence the rejection thereof under 35 USC 112, first paragraph, on this ground, should be withdrawn.

The Examiner again rejected claims 1, 6 to 19 and 36 to 38 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Reconsideration is requested, having regard to the revisions to the claims and the following comments.

The Examiner considered claim 1 to be indefinite with respect to the recitation of the first, second and third DNA sequences being under the transcriptional control of a promoter. The Examiner considered it unclear whether the DNA sequences were all linked to one promoter or if they are operatively linked to their own promoter.

In this regard, claim 1 has been amended to recite a single promoter, clarifying that the DNA sequences are all under control of the same promoter. It is submitted that claim 1 can no longer be considered indefinite in this respect.

The Examiner considered claim 1 to be indefinite on the basis that he considered it unclear whether the phrase "and that enhances the immunoprotective ability of the RSV protein as fragment thereof" refers to the first or third DNA sequence. Claim 1 has been amended to recite that is the third DNA sequence which enhance the immunoprotective ability. It is submitted that claim 1 can no longer be considered indefinite in this respect.

The Examiner indicates the structure of the third DNA sequence is unclear and how the recitation of a third sequence in claim 11, claim 12 and claim 13 correlate to the third sequence of claim 1. Claim 11 has been deleted, as noted above. Claim 1 has been amended to recite that the third DNA sequence is located between the first DNA sequence and the promoter, as previously recited in claim 13, which has been deleted. Claim 1 has been further amended to recite that the third DNA sequence comprises a pair of splice sites that prevent aberrant mRNA splicing *in vivo*, as previously recited in claim 12, which has been deleted.

Claim 14 has been made dependent on claim 1 and the language has been modified to clarify that the third sequence recited in claim 1 is the same as recited in claim 14, by referring in claim 14 to a third DNA sequence. Claim 15 also have been amended to refer to the third DNA sequence.

It is submitted that the nature of the third DNA sequence is quite clear as is the interrelationship of the third DNA sequence as recited in claim 1 and in the subclaims.

The Examiner's objection to claim 11 as remaining indefinite in several respects is rendered moot by cancellation of this claim.

The Examiner considered the phrase "to enhance the immunoprotective ability of a paramyxovirus protein" as used in claim 1 to be indefinite. The language actually used in claim 1 refers to the RSV proteins or fragments. As discussed above with respect to the rejection under 35 USC 112, first paragraph, applicants have demonstrated a significant level of protection to be achieved using pMP44 in contrast to the prior art, thereby demonstrating the ability to enhance the immunoprotective ability of the protein. It is submitted that claim 1 is not indefinite in this respect.

The Examiner considered the term "aberrant mRNA splicing *in vivo*" as used in claim 12 to be indefinite. This phrase now is recited in claim 1. It is submitted that it is clear in the context of the claim and the specification that applicants are simply reciting that aberrant mRNA splicing does not occur when the vector is used *in vivo*. It is submitted that claim 1 is not indefinite in this respect.

The Examiner indicates that it is unclear how the location of the third nucleotide sequence as described in claim 13 correlates to the first, second or third sequence recited in claim 12 or claim 1. In this respect, as noted above, the claims now consistently refer to DNA sequences. It is submitted that there is no remaining indefiniteness in this respect.

The Examiner considered the term "immunoeffective amount" in claim 36 to be indefinite. The term simply refers to the amount sufficient to achieve an immune response. In the interests of advancing prosecution, the offending phrase has been deleted from claim 36. It is submitted that claim 36 no longer can be considered indefinite.

Having regard to the revisions made to the claims and the above comments, it is submitted that claims 1, 6 to 19 and 36 to 38, insofar as they remain in the application and in their amended form, can no longer be considered indefinite and hence the rejection under 35 USC 112, second paragraph, should be withdrawn.

The Examiner maintained rejection of claims 1, 6 to 16, 18, 36 and 37 under 35 USC 102(e) as being anticipated by Parrington. Reconsideration is requested having regard to the following comments.

For these to be anticipation, the reference must disclose every element of the claim considered to be anticipated. Parrington does not describe a vector as claimed in amended claim 1. While Parrington discloses a vector containing the first DNA sequence, the second DNA sequence and the promoter recited in claim 1, Parrington does not disclose such a vector containing the third sequence as recited in claim 1. In particular, while Parrington discloses a vector containing a DNA sequence which is complementary to at least part of an alphavirus RNA genome, a DNA sequence encoding RSV F or G protein or fragment and a promoter operatively connected to these DNA sequence, Parrington does not disclose, in any such vector, a third DNA sequence located between the first DNA sequence and the promoter and comprising a pair of splice sites as recited in claim 1.

The Examiner states in the Final Action that:

> "Parrington teach a Semliki forest viral vector expressing the F or G proteins of RSV. The sequence contains the CMV immediate early promoter and rabbit β-globin intron II (col. 4, line 11)."

The first sentence of this statement is correct while the second is not. As previously explained col. 4, line 11, to which the Examiner refers, is discussing the content of WO 96/40945, i.e., the Li et al reference cited by the Examiner and the vector which is described therein. While the Li et al vector contains the rabbit β-globin intron II sequence, the Li et al reference does not employ a Semliki virus sequence ("first DNA sequence"). There is no disclosure in Parrington of a vector containing the β-globin intron II sequence ("third DNA sequence").

In addition, it is noted that claims 18 and 37, both of which recite the vector pMP44, were included in the rejection. It is absolutely clear that Parrington does not describe construction of any such plasmid.

Having regard to the above, it is submitted that claims 1, 6 to 16, 18, 36 and 37, insofar as they remain in the application and in their amended form are not anticipated by Parrington and hence the rejection should be withdrawn.

The Examiner maintained rejection of claims 1, 6 to 16, 18 and 36 and 37 under 35 USC 103 as being "anticipated by" Dubensky in view of Li et al. It is believed the Examiner intended to state "unpatentable over" rather than "anticipated by". Reconsideration is requested having regard to the following comments.

In the Final Action, the Examiner indicates that:

> "Dubensky teach an alphaviral vector encoding RSV proteins (claim 10 of '482). The alphaviral vector sequence is the "first DNA sequence" and the DNA encoding the RSV protein is the "second DNA sequence" and "third DNA sequence" as claimed. The alphavirus of Dubensky is Semliki forest virus (col. 11, line 67) which is equivalent to the sequence contain in plasmid pSFVI (claim 9)."

It is not seen how the DNA encoding the RSV protein can be considered to be the "third DNA sequence" recited in claim 1 as well as being the "second DNA sequence". They are discrete sequences, otherwise there would be no need to recite them separately.

In addition, claim 1 has been amended, as discussed above, to recite that the third DNA sequence is located between the promoter and the second DNA sequence and that the sequence comprises a pair of splice sites to prevent aberrant mRNA splicing. To further clarify that the DNA encoding RSV cannot comprise the third sequence, claim 1 has been further amended to recite that the second DNA sequence is downstream of the first DNA sequence.

The Examiner further recites in the Final Action that:

> "The limitation of a third sequence operatively linked to the first DAN sequence (claim 1) is equivalent to the DNA encoding the RSV proteins because the phrase "that enhances the immunoprotective ability ...." Is indefinite (see 112/2nd above) and is an intended use which does not have to occur. As such the phrase "that enhances the immunoprotective ability...." Is not given patentable weight in considering art."

As already discussed above, the enhancement of immunoprotective ability is not indefinite and subject to rejection under 35 USC 112, second paragraph. Rather the recitation is a functional recitation of the structure of the third DNA sequence. The recitation is not an "intended use", as suggested by the Examiner but a recitation of how the element functions under a specific set of circumstances. In addition, claim 1 now recites that the third DNA sequence comprises a pair of splice sites which have the function of preventing aberrant mRNA splicing *in vivo*. Thus, the third DNA sequence recited in claim 1 has specific structure and function. There is no such element described in Dubensky. Despite the Examiner's urging to the contrary, there

is no structure described in Dubensky which has the same structure and function as applicants third DNA sequence.

As the Examiner indicates, Dubensky does not teach the nucleic acid sequence of RSV F or G proteins. The Examiner relies on Li et al to make up this deficiency. Whether or not, having regard to the Li et al disclosure, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the expression vector encoding RSV protein taught by Dubensky to deliver the F and G proteins taught by Li, is immaterial, since neither reference discloses any DNA sequence which corresponds to applicants third DNA sequence having the structure and function recited in claim 1.

As discussed above, the Li et al reference discloses a CMV promoter and a rabbit β-globin intron II sequence in a DNA construct. However, as discussed above, neither of these elements is suggested for incorporation into a Semliki virus or other alphavirus vector.

It is noted that the Examiner has not included claims19 and 38, directed to a specific SEQ ID NO: nucleotide sequence, in this rejection. Having regard thereto, there appears to be no logical reason to include claims 18 and 37, directed specifically to pMP44 having such sequence, in this rejection.

Having regard to the above, it is submitted that claims 1, 6 to 16, 18, 36 and 37, insofar as they remain in the application and in their amended form are patentable over the applied art and hence the rejection thereof under 35 USC 103 as being unpatentable over Dubensky in view of Li et al, should be withdrawn.

The Examiner maintained rejection of claims 1, 6 to 16, 18, 36 and 37 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 3, 5, 6, 8 and 18 to 21 of USP 6,060,308.

The relationship of the claims of this application as amended to U.S. Patent No. 6,060,308 has been discussed above with respect to the rejection based upon this reference under 35 USC 102(e). It is submitted, from that discussion, that the claims of this application are patentably distinct from the claims of U.S. Patent 6,060,308.

In the Final Action, the Examiner refers to the pMP37 vector, which is provided in USP 6,060,308. Elements from this vector are used in the assembly of

pMP44. However, pMP44 contains structural elements additional to those contained in pMP37. It is not true to say, as the Examiner asserts in the Final Action, that:

> "... the vectors of claims 1 to 3, 6, 8 and 18 to 21 of US Patent No. 6,060,308 are vectors as claimed in the instant application."

Since the vectors of the present application contain additional elements.

Accordingly, it is submitted that claims 1, 6 to 16, 18, 36 and 37 do not represent an obviousness-type double patenting of claims 1 to 3, 5, 6, 8 and 18 to 21 of Parrington USP 6,060,308.

Entry of this Amendment after Final Action is requested in that the application thereby is placed in condition for allowance. In the event the Examiner considers one or more ground of rejection to remain, this Amendment nevertheless should be entered, since the issues for appeal thereby are reduced and/or the claims are placed in better condition for appeal.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

It is believed that this application is now in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,

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Appl. No. 09/190,246

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 7, 11, 12 and 13 have been cancelled.

Claims 1, 14, 15 and 36 have been amended as follows:

1. (Twice Amended) A vector, comprising:

a first DNA sequence which is complementary to at least part of an alphavirus RNA genome and having the complement of complete alphavirus RNA genome replication regions that permits *in vivo* replication;

a second DNA sequence encoding a respiratory syncytial virus (RSV) protein selected from the group consisting of the F and G glycoprotein of RSV or encoding a [an] protein fragment that induces production of antibodies that specifically react with the RSV protein, said protein fragment being a truncated RSV F or RSV G protein lacking the transmembrane anchor and cytoplasmic tail, said second sequence being downstream of said first sequence; and

a third DNA sequence operatively linked to the first DNA sequence, said third DNA sequence enhancing [and that enhances] the immunoprotective ability of the RSV protein or fragment thereof when expression occurs *in vivo*, said first, second and third DNA sequences being under transcriptional control of a single promoter, said third DNA sequence being located between said first DNA sequence and the promoter sequence and comprising a pair of splice sites that prevent aberrant mRNA splicing *in vivo*.

14. (Amended) The vector of claim 1 [13] wherein said third DNA [nucleotide] sequence is that of rabbit β-globin intron II.

15. (Twice Amended) The vector of claim 1 wherein said promoter sequence is an immediate early cytomegalovirus (CMV) promoter and the human cytomegalovirus Intron A sequence is provided downstream of the promoter and upstream of the third DNA [nucleotide] sequence.

36. (Amended) An immunogenic composition comprising [an immunoeffective amount of] a vector of claim 1.